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Title: HORMONAL CONTRACEPTIVE

Abstract: The invention relates to a hormonal contraceptive with two hormonal components. The contraceptive comprises at least one gestagen and a second hormonal component containing at least one estrogen, for continuous and combined administration. The inventive contraceptive guarantees high contraceptive efficiency and reliable suppression of the menstrual cycle.

Hormonal Contraceptive

This invention concerns a hormonal contraceptivewith two hormonal components, its use and a procedure for hormonal contraception.

Since hormonal contraceptives began to be available in the 1960s, a great number of hormonal components have been investigated for their suitability in widely varied administration schemes. They may basically be divided into combined and sequential preparations.

In combined preparations, for example, if the desired cycle length is 28 days, a combination of an estrogen preparation and a gestagen preparation is administered for 21 days in a constant or changing absolute and/or relative dosage, with the estrogen preparation being natural estrogen or synthetic ethinyl estradiol, and with the taking of the aforementioned 21 daily units being followed by a seven-day interval in which withdrawal bleeding occurs that simulates natural monthly bleeding.

In sequential preparations, again with a desired cycle length of 28 days, a pure estrogen preparation is administered for 7 days and then a combination of an estrogen preparation and a gestagen preparation for 15 days, followed again by a no-administration period of 6 days, for example, in which there is withdrawal bleeding. In the interests of greater administration reliability, placebos have been administered on the days involved to span the no-administration intervals characteristic of the combined and sequential preparations, but it has always been hitherto assumed that, in order to guarantee reliable withdrawal bleeding, no hormones of the type being discussed here must be administered during the approximately one-week no-administration interval.. Only in replacement preparations in the menopause of older women have hormones been administered throughout the entire cycle, for example, in the sequence of 10 days of an estrogen preparation, 11 days of a combination of an estrogen and a gestagen preparation, 7 days of an estrogen preparation, and 7 days of an estrogen preparation in an especially low dose, but these replacement preparations are not suitable for inhibiting ovulation.

The sequential preparations used in replacement therapy are therefore particularly unsuitable for contraception since natural estradiol does not prevent ovulation at the dosage given and the phase in which gestagen is administered is too short at only 11 days. The sequential arrangement described above does, however, guarantee relatively good cycle control in the case of replacement preparations.

A combined preparation for contraception is known from German patent DE-PS 43 08 406 consisting of one or more steps. This provides that at least one step contains the combination of three components, i.e., a biogenic estrogen, a synthetic estrogen and a gestagen, and the other steps each consist of a pharmaceutically harmless placebo or a biogenic or synthetic gestagen, or a biogenic or synthetic estrogen, or a combination of two components, i.e., a biogenic estrogen, a synthetic estrogen and a gestagen or a combination of synthetic estrogen and a gestagen.

It can be seen from the specification of the above patent that there is typically a change in state over time with the step concept described therein. This kind of change of state may result both from the fact that the composition of the phases making up the step

changes in terms of the components used and also from the fact that only the concentrations of the components used in the phases making up the step change.

This invention is based on the problem of producing a hormonal contraceptive which guarantees great contraceptive reliability and excludes intermediate bleeding. The side effects observed in hormonal contraceptives are also to be further reduced.

This invention solves this problem by a hormonal contraceptive with two hormonal components, with the contraceptive comprising an initial hormonal component comprising at least one gestagen and a second hormonal component comprising at least one estrogen, for continuous and combined administration.

The problem is further solved by a procedure for hormonal contraception in which a contraceptive comprising at least a first hormonal component comprising at least one gestagen, and a second hormonal component comprising an estrogen, is continuously adminstered.

Another aspect of the invention involves the use of the contraceptive of the invention for inhibiting ovulation.

Another aspect of the invention involves the use of the contraceptive of the invention for the treatment and/or prophylaxis of tumors of the mammary glands.

In another embodiment, the invention proposes that the gestagen used as the first hormonal component be selected from the group made up of progesterone, chlormadinone acetate, norethisterone acetate, cyproterone acetate, desogestrel, levonorgestrel, other natural and/or synthetic gestagens, antigestagens and hormone analogs with a gestagenic or antigestagenic action, as well as hormone compounds which rapidly split off at least one gestagen after intake.

The contraceptive of the invention may provide for the estrogen used as the second hormonal component to be selected from the group made up of synthetic estrogens, biogenic estrogens, antiestrogens and hormone analogs with an estrogenic or anti-estrogenic action.

In a preferred embodiment, the synthetic estrogen is selected from the group made up of ethinyl estradiol, mestranol and others as well as hormone compounds that rapidly split off a synthetic estrogen after intake.

Ethinyl estradiol is especially preferred as the synthetic estrogen.

In preferred embodiments, the amount of ethinyl estradiol administered dally can be 1 to 20 µg.

An amount of ethinyl estradiol administered daily of 5 to 10 µg is especially preferred.

In accordance with the invention, the biogenic estrogen can be selected from the group made up of estradiol, estriol, estrone, estrane and others, as well as hormonal compounds which rapidly split off at least one biogenic estrogen after intake.

In one embodiment, estradiol includes 17-α-estradiol and/or 17-β-estradiol.

In another embodiment, the amount of biogenic estrogen administered daily in the case of estradiol, and especially α- and β-estradiol, can be 0.1 to 2 mg, and in the case of conjugated estrogens can be 0.05 to 0.5 mg.

In one embodiment, the contraceptive of the invention may be provided for oral administration.

In an alternative embodiment, the contraceptive of the invention may be provided for transdermal administration.

In a second alternative embodiment, the contraceptive of the invention may be provided for intravaginal administration.

In a third alternative embodiment, the contraceptive of the invention may be provided as a depot injection.

In a fourth alternative embodiment, the contraceptive of the invention may be provided for administration as a hormone implant.

Finally, daily units each comprising both hormonal components, can be arranged with spatial separation to be individually removable in one packaging unit.

In one embodiment of the procedure of the invention, the first hormonal component can be administered combined with the second hormonal component.

In another embodiment, the procedure of the invention can finally provide for administration of the contraceptive of the invention.

The invention is based on the surprising knowledge that high contraceptive efficiency can be achieved by continuous and combined administration of a contraceptive consisting of two hormonal components, i.e., a first hormonal component comprising at least one gestagen and a second hormonal component comprising at least one estrogen.

Estrogens are to be taken herein to mean, according to the current interpretation, steroid molecules which develop their action preferably by exerting a biological action at various places in the cell in various organs in a varying manner. Estrogens may act on (1) the cell membrane, (2) intracellular cytoplasmatic proteins and (3) specific cell nucleus receptors. It has recently become known that, in addition to the classic type 1 estrogen receptor, a second type 2 estrogen receptor has been described for which the organ distibution is different from that of the type 1 estrogen receptor.

The above definition thus also includes those compounds termed "designer hormones" which manifest the properties given above.

Biogenic estrogens are therefore steroid molecules which develop an estrogen-like action on the membrane, on cytoplasmatic proteins and on nucleus receptors for

hydrophobic ring substances and thereby trigger biological actions which correspond to a hydrophobic steroid ring structure capable of triggering estrogen-like actions in cells, organs and the entire body.

Biogenic estrogens are also to be taken to mean those estrogens which are produced by the human body and therefore include the body's own estrogens. The biogenic estrogens used in certain embodiments of the contraceptive of the invention are typically those which are chemically synthesized. Basically, however, the use of such compounds isolated from a body is also possible.

Furthermore, biogenic estrogens are to be taken herein also to mean conjugated biogenic estrogens such as, for example, estradiol valerate and estrone sulfate.

Antiestrogens are to be taken herein to mean hydrophobic ring structure substances and other substances which can specifically and selectively counteract the estrogen activity described above again on cells, organs or in the entire body.

Continuous administration is taken herein to mean an administration that is uninterrupted over the period of application in which no no-administration intervals are provided with respect to the hormonal components. This also means that there is no interruption of the administration of the contraceptive by administering placebos instead of the hormonal contraceptive. There are subsequently no changes in the basic composition of the hormonal components for the entire time of administration that typically encompasses a period of several months to years. Instead, the hormonal components making up the hormonal contraceptive of the invention are administered uninterrupted and unchanged in an unchanged concentration for the entire time of administration. It is conceivable, however, that the concentration of the estrogen, understood in the wide sense of the term herein defined, and gestagen, also understood in the wide sense of the term herein defined, may be changed in the case of older women compared to younger women. This may also happen in such a way that throughout the continuous application, one starts first with a given composition and adapts this composition in the course of weeks, months and years to the changed needs of the woman by applying a subsequent preparation which, however, also comprises a contraceptive as defined in this invention.

The continuous application of the cited hormonal components guarantees that the hormonal processes naturally occurring in the female body do not impair contraceptive reliability.

The estrogen component or the specific activity of hydrophobic ring substances with an estrogen-like action may cause gonadotrophin suppression. This is desirable. The consequent suppression of ovarian function is balanced out by an adequate replacement of estrogen activity. This prevents the development of osteoporosis, maintains the favorable vascular effects of estrogens and does not adversely affect lipid metabolism. Interruption of cycle-dependent instability in the hormonal system can have a favorable effect on premenstrual syndrome, and the hemostasis of the coagulation system is not disturbed since the labile equilibrium in which the coagulation system exists is not activated and deactivated by the ups and downs of the hormonal fluctuations. The hormonal contraceptive of the invention is therefore also especially suitable for women over 40 years of age in whom the danger of breakthrough bleeding

disturbances is known to increase with age. This reduces the risk of thrombosis which has recently become highly significant in contraceptive therapy.

It has also surprisingly been discovered that administration of the contraceptive of the invention makes possible reliable continuous suppression of the menstrual cycle and monthly bleeding at a very low dosage. Without wishing to be hereinafter pinned down to this issue, the combination of the two hormonal components cited, and especially the low dosage of the estrogen therein, appears to eliminate the otherwise normal side effects of ethinyl estradiol and to remain below the application of more than 15 µg ethinyl estradiol typically required with contraceptives according to the prior art.

The low dosage of the two hormonal components and especially the estrogen component is made possible by the additive effect of the two hormonal components, without any impairment of the effect of the contraceptive of the invention in terms of its contraceptive and ovulation-inhibiting properties.

The ovulation inhibition and suppression of the menstrual cycle reliably guaranteed by the contraceptive of the invention are highly significant for certain patients, such as, for example, serious athletes, dancers and business women who wish to avoid any impairment of their physical, mental and emotional performance due to their menstrual cycle. The combined and continuous administration of the two hormonal components of the contraceptive of the invention makes it possible to administer it orally, transdermally, intravaginally, by depot injections or by hormone implants. This allows the advantages observed for the pertinent application forms to be realized in the case of the contraceptive of the invention.

All forms known in the prior art such as, for example, tablets, coated tablets, pills or capsules produced using the standard adjuvants and vehicles may be used as oral forms of administration.

For transdermal administration of the contraceptive of the invention, the two hormonal components making up the contraceptive may be applied to a plaster, for example, or may also be applied by means of transdermal therapeutic systems and thus supplied to the body, with, for example, an already prepared combination of the two hormonal components or the two components being individually put into a system of this kind based on iontophoresis or diffusion or, optionally, a combination of these effects.

In the case of oral application, it has proven useful for daily units which comprise a combination of the two hormonal components in each case to be arranged spatially separated and individually removable in a packaging unit, so that it is easy to check whether the oral preparation form to be typically taken on a daily basis has in fact already been taken or not. It is important to ensure that there are no no-administration days. Depot injections may be applied at intervals of 1 to 6 months or even longer. Hormone implants contain both hormonal components and release them for a period of preferably 3 to 6 months.

In the application of the contraceptive of the invention it has further been surprisingly discovered that it may be used in the treatment and/or prophylaxis of tumors of the mammary glands. It has recently been recognized by research into the risk of breast cancer that this cancer occurs when there are mutations in certain risk genes that may

be congenital or acquired. Modern cancer therapy assumes that a cancer-triggering mutation that can still first be controlled by the other healthy allele is present on one of the two alleles of a gene. If there is also another mutation in the course of life on the second allele in a certain organ cell, this cell can become subject to uncontrolled malignant growth.

Mutations on the second allele occur especially frequently at certain phases of the cell cycle, i.e., in the so-called G1 phase. The menstrual cycle drives the breast cell every four weeks into a cell cycle, and "opens" the genome for mutations which are either repaired or apoptotically "removed". Under the conditions of classic combined or sequential contraceptive treatment, a woman can have 500 to 700 cycles during her life, while under natural conditions a woman has a maximum of 20 to 30 cycles. Thus a substantial risk of mutation is carried into the stimulated mammary gland tissue in an unusually abundant number of cell cycles over 8 days in each case. If the menstrual cycle is suppressed, as is possible with the contraceptive of the invention, the mammary cells are brought into a "rest phase" and it is scientifically confirmed that fewer cancer-causing mutations get into a tissue in the rest phase than in a stimulated tissue. This reduces mutagenesis, i.e., the risk of breast cancer, by a large factor.

The above use of the contraceptive of the invention for the treatment and/or prophylaxis of tumors of the mammary glands is, then, especially associated with very special advantages if users of the contraceptive are high-risk carriers like, for example, those with a family history of breast cancer.

The amount of the estrogens and gestagens administered essentially corresponds to the amount of comparable preparations in the prior art. More data on the daily amounts of different compounds making up the first and second hormonal component to be administered can be found in the examples.

The invention is further illustrated below by means of examples of embodiment which provide more features, advantages and embodiments of this invention.

Example 1:

A contraceptive was used for contraceptive treatment which contains 5 µg ethinyl estradiol and 2 mg norethisterone acetate per daily unit in tablet form. It is notable that norethisterone acetate can be applied in a concentration range of 0.5 to 5 mg. The contraceptive was administered for 9 months and showed very good contraceptive reliability with complete suppression of the menstrual cycle and practically no side effects. In the investigation presented here it was established that the subjects took the contraceptive daily, i.e., with no tablet-free period, for the entire period cited above.

Example 2:

A contraceptive was used for contraceptive treatment which contains 0.5 mg estriol and 2 mg chlormadinone acetate per daily unit in tablet form. It is notable that estriol can be applied in a concentration range of 0.5 to 3 mg and chlormadinone acetate in a concentration range of 0.75 to 5 mg. The contraceptive was administered for 12 months with no tablet-free period. The type of effect corresponded to that in example 1.

Example 3:

A contraceptive was used for contraceptive treatment which contains 0.5 mg estradiol valerate and 2 mg lynestrenol per daily unit in tablet form. It is notable that estradiol valerate can be applied in a concentration range of 0.5 to 5 mg and lynestrenol in a concentration range of 0.5 to 4.5 mg. The contraceptive was administered for 12 months with no tablet-free period. The type of effect corresponded to that in example 1.

Example 4:

A contraceptive was used for contraceptive treatment which contains 7.5 µg ethinyl estradiol and 75 µg desogestrel per daily unit in tablet form. It is notable that desogestrel can be applied in a concentration range of 50 to 200 µg. The contraceptive was administered for 12 months with no tablet-free period. The type of effect corresponded to that in example 1.

Example 5:

A contraceptive was used for contraceptive treatment which contains 20 mg tamoxifen and 2 mg lutenyl per daily unit in tablet form. It is notable that tamoxifen can be applied in a concentration range of 10 to 50 mg and lutenyl in a concentration range of 1 to 5 mg. This contraceptive is best suited to women with a family history of breast cancer risk. The contraceptive was administered for 12 months with no tablet-free period. The type of effect corresponded to that in example 1.

Example 6:

A contraceptive was used for contraceptive treatment which contains 50 mg raloxifen and 2.5 mg medroxyprogesterone acetate (MPA) per daily unit in tablet form. It is notable that raloxifen can be applied in a concentration range of 30 to 100 mg and

medroxyprogesterone acetate in a concentration range of 2 to 10 mg. This combination is best suited to women with a family history of breast cancer risk and to young women surviving breast cancer. The contraceptive was administered for 12 months with no tablet-free period. The type of effect corresponded to that in example 1.

Example 7:

A contraceptive was used for contraceptive treatment which contains 10 µg ethinyl estradiol and tibolone in a concentration of 2 mg daily per daily unit in tablet form. It is notable that tibolone can be applied in a concentration range of 1 to 10 mg. The contraceptive was administered for 12 months with no tablet-free period. The type of effect corresponded to that in example 1.

Example 8:

A contraceptive was used for contraceptive treatment which contains 10 µg ethinyl estradiol and, as an antigestagen, the substance Ro486 in a concentration of 2.5 mg per daily unit in tablet form. It is notable that Ro486 can be applied in a concentration range of 1 to 7.5 mg. The contraceptive was administered for 12 months with no tablet-free period. The type of effect corresponded to that in example 1.

The features of the invention disclosed in the above description and in the claims may be essential both individually and in any desired combination for the realization of the invention in its different embodiments.

Claims

1. Hormonal contraceptive with two components, characterized in that the contraceptive comprises a first hormonal component comprising at least one gestagen and a second hormonal component comprising at least one estrogen, for continuous and combined administration.

2. Contraceptive as in Claim 1, characterized in that the gestagen is selected as the first hormonal component from the group consisting of progesterone, chlormadinone acetate, norethisterone acetate, cyproterone acetate, desogstrel, levonorgestrel, other natural and/or synthetic gestagens, antigestagens and hormone analogs with a gestagenic or antigestagenic action, as well as hormone compounds which rapidly split off at least one gestagen after intake.

3. Contraceptive as in Claim 1 or 2, characterized in that the estrogen is selected as the second hormonal component from the group consisting of synthetic estrogens, biogenic estrogens, antiestrogens and hormone analogs with an estrogenic or antiestrogenic action.

4. Contraceptive as in Claim 3, characterized in that the synthetic estrogen is selected from the group consisting of ethinyl estradiol, mestranol and others, as well as hormone compounds which rapidly split off at least one synthetic estrogen after intake.

5. Contraceptive as in Claim 4, characterized in that the synthetic estrogen is ethinyl estradiol.

6. Contraceptive as in Claim 5, characterized in that the amount of ethinyl estradiol administered daily is 1 to 20 µg.

7. Contraceptive as in Claim 6, characterized in that the amount of ethinyl estradiol administered daily is 5 to 10 µg.

8. Contraceptive as in any of Claims 3 through 7, characterized in that the biogenic estrogen is selected from the group consisting of estradiol, estriol, estrone, estrane and others, as well as hormone compounds which rapidly split off at least one biogenic estrogen after intake.

9. Contraceptive as in Claim 8, characterized in that the estradiol comprises 17-α-estradiol and/or 17-β-estradiol.

10. Contaceptive as in any of Claim 3 through 9, characterized in that the amount of biogenic estrogen administered daily in the case of estradiol, and especially α- and β-estradiol, is 0.1 to 2 mg and in the case of conjugated estrogens 0.05 to 0.5 mg.

11. Contraceptive as in any of Claims 1 through 10 for oral administration.

12. Contraceptive as in any of Claims 1 through 10 for transdermal administration.

13. Contraceptive as in any of Claims 1 through 10 for intravaginal administration.

14. Contraceptive as in any of Claims 1 through 10 for administration as a depot injection.

15. Contraceptive as in any of Claims 1 through 10 for administration as a hormone implant.

16. Contraceptive as in any of Claims 1 through 15, characterized in that daily units each consisting of the two hormonal components are arranged spatially separate and are individually removable in a packaging unit.

17. Use of the contraceptive as in any of Claims 1 through 16 for ovulation inhibition.

18. Use of the contraceptive as in any of Claims 1 through 16 for the treatment and/or prophylaxis of tumors of the mammary glands.

19. Procedure for hormonal contraception, characterized in that a contraceptive comprising at least a first hormonal component comprising at least one gestagen, and a second hormonal component comprising at least one estrogen, is administered continuously.

20. Procedure as in Claim 19, characterized in that the first hormonal component is administered in combination with the second hormonal component.

21. Procedure as in Claim 19 or 20, characterized in that a contraceptive as in any of Claims 1 through 16 is administered.